REMARKS

Claims 13-42 are in the case. Claim 13 has been amended. Claims 14-34 remain unchanged. Claims 35-42 have been added by amendment. No new matter has been introduced.

Applicant first wishes to thank the Examiner for the courteous interview conducted on September 17, 2002, with Applicant's representative, Ms. Leber, and Drs. Summersell and Trofast.

During the interview, the Examiner's supervisor questioned whether a method involving "instructing a patient" constitutes statutory subject matter. Applicant submits that the claims do constitute statutory subject matter under 35 U.S.C. §101. As explained by the Federal Circuit in *In re Alappat*,

> The use of the expansive term "any" in §101 represents Congress's intent not to place any restrictions on the subject matter for which a patent may be obtained beyond those specifically recited in §101 and the other parts of Title 35. *In re Alappat*, 33 F.3d 1526, 1542.

The Supreme Court has held the excluded categories of subject matter, which are not entitled to patent protection, are: laws of nature, natural phenomena, and abstract ideas. *Ibid.* The subject matter of the instant claims does not fall into any of these excluded categories, and thus is entitled to patent protection.

Claims 13-34 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Carling in view of Vanzieleghem et al. (Vanzieleghem) and Sykes et al. (Sykes).

In the office action, the Examiner noted that Carling teaches that dosage depends on the patient (age, weight, etc.) and the severity of the disease (mild, moderate, severe, etc.), and stated that "Applicant has not demonstrated or set forth any reason for the criticality of" the claimed "on demand" administration.

During the interview, Ms. Leber and Dr. Trofast explained that Carling does not teach or suggest that the medicine be used "on demand" to provide both treatment and prevention of future asthma exacerbations.[1] In the following discussion, Applicant will provide some

[1] As noted by Ms. Leber at the interview, subsequent to Applicant's response to the previous office action, Applicant noticed that Carling does mention, in addition to fixed dosing, use of the Carling composition as a rescue medicine. However, this use is only mentioned in passing at p. 4, line 8, and there is no suggestion that the composition be used on demand to prevent future exacerbations.

background concerning the understanding of asthma treatment prior to Applicant's invention, an explanation of why the claimed treatment protocol is surprising in view of the conventional wisdom at the time of Applicant's invention, and a discussion of the benefits of the claimed treatment protocol.

Asthma is a chronic inflammatory disease of the airways. In July 1997, the National Institute of Health (NIH) published an Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (NIH Publication No 97-4051, "The NIH Guidelines"). The NIH Guidelines clearly describe what was known about asthma and asthma treatment at the time. They emphasize that persistent asthma requires both (a) long-term daily therapy to decrease the frequency and severity of asthma symptoms, and (b) appropriate medications to manage asthma episodic attacks. (Declaration of Christer Hultquist, submitted herewith, paragraph 2.)

Acute attacks are defined as medical emergencies and should be regarded as a failure in the long-term management of the disease. The severity of an attack of acute asthma (exacerbations of asthma in the home, in the emergency room, and in the hospital) is often underestimated by patients, their relatives and their doctors, largely because of failure to make objective measurements. If not recognized or not treated appropriately, such attacks can be fatal (M. Woodhead in "Guidelines on the management of asthma," Thorax 48 (1993), supplement S1-S24). Acute attacks demand immediate medical treatment with a medicament having fast onset of action, to rapidly alleviate the attack. (Declaration of Christer Hultquist, paragraph 3.)

The NIH Guidelines categorized asthma medications into two general classes:

(1) long-term-control medications, which are taken daily on a long-term basis to achieve and maintain control of persistent asthma (also known as long-term preventive, controller, or maintenance medications), and

(2) quick relief medications, which are taken during acute attacks and at other times when prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction is needed (also known as reliever, rescue, or acute rescue medications). (Declaration of Christer Hultquist, paragraph 4.)

Quick relief medications are prescribed for inhalation when the patient experiences, or expects to experience, an acute attack. These medicines provide short-term bronchodilation. They do not reduce airway inflammation. The dosage regimen for these medications is not fixed,

but instead the patient is instructed to use the medication for symptomatic relief as needed, e.g., in the event of an acute attack. Prior to Applicant's invention, short-acting bronchodilators, for example, the short-acting β_2-agonists salbutamol (albuterol) and terbutaline, were the only products recommended for use on an "as needed" or "on demand" basis. (Declaration of Christer Hultquist, paragraph 5.)

Long-term-control medications for maintenance treatment are prescribed for inhalation on a regular basis, typically one or more times each day, with a fixed number of doses being inhaled at each use. For example, U.S. Patent No. 5,674,860 (Carling) discloses administering budesonide/formoterol at a recommended dose regimen of twice daily (col. 3, line 43). These medicines are used to gradually reduce bronchial inflammation and thereby reduce the frequency and severity of asthma symptoms. Long-term-control medications are typically steroids. (Declaration of Christer Hultquist, paragraph 6.)

As discussed in Carling, the dosage regimen for a maintenance medication may differ from patient to patient (col. 3, lines 44-49), depending on factors such as body weight and the physician's diagnosis of the severity of the patient's asthma. However, *for a particular patient the dosage regimen remains fixed*, i.e., the amount the patient is to inhale daily remains the same from day to day. The patient is instructed not to vary the dosage regimen without first consulting the patient's physician. If the patient experiences a change in symptoms, e.g., increased symptoms, or more frequent or more severe acute attacks, the patient must arrange an appointment with his or her physician to discuss a change in the dosage regimen. Before a drug is registered, e.g., by the FDA, it is carefully investigated for safety, and as a result of these investigations the drug is labeled to indicate how the drug should be prescribed and used. It is the responsibility of the physician to prescribe a safe dose regimen that is in accordance with the labeling and to instruct the patient to follow this regimen. Physicians do not instruct patients to take a medication "on demand" unless the medication is approved and labeled for such use, due to safety concerns, e.g., concerns with side effects, build-up of the drug in the body, and interactions with other drugs. (Declaration of Christer Hultquist, paragraph 6.)

Because it is often inconvenient for the patient to consult with his or her physician, patients may tend to put off doing so. The physician cannot know that the patient's symptoms are not being properly controlled unless the patient tells the physician, and thus, absent this

communication, the physician cannot remedy any problems with the patient's maintenance treatment. As a result, due to a reluctance or inability to visit the physician, the patient may continue to receive an inadequate dose of inhaled steroid. (Declaration of Christer Hultquist, paragraph 7.)

Inadequate maintenance treatment, due to the patient's not inhaling a sufficient dosage of inhaled steroids, may result in an acute attack. During an acute attack, the patient usually takes a short-acting β_2-agonist as a quick relief medication, as discussed above. Such a medication does nothing to treat airway inflammation or prevent future exacerbations. (Declaration of Christer Hultquist, paragraph 8.)

According to the present invention, a patient is instructed to take the claimed formoterol/budesonide combination "on demand," when the patient needs symptomatic relief, for example, when the patient is or has recently been experiencing an increase in asthma symptoms. When the combination is inhaled, the patient simultaneously inhales both types of medications (budesonide for long-term-control and formoterol for quick relief). Thus, each time the formoterol/budesonide combination is inhaled by the patient, the patient obtains an extra dose of steroid. In this manner, the patient simultaneously receives both immediate relief of bronchial obstruction and anti-inflammatory treatment. The treatment is thus both immediate, providing a rapid decrease in airway obstruction, *and preventive*, providing a long-term decrease in airway inflammation. This long-term decrease in airway inflammation will tend to prevent future asthma exacerbations, which in turn will tend to reduce the overall level of asthma medication needed by the patient. (Declaration of Christer Hultquist, paragraph 9.)

Recent research supports the viability of Applicant's claimed method of asthma treatment. For instance, a dose-response relationship has been shown for both budesonide and formoterol within the approved dose-range of the monoproducts (Ind et al., European Respiratory Society Annual Congress (ERS) Stockholm, September 14-18, 2002; poster P2450 (Appendix 2) and Rosenhall et al., (ERS), Stockholm, 2002, poster P388 (Appendix 3)).

Moreover, Ankerst et al. have recently shown that a combination of budesonide/formoterol in a single inhaler is well tolerated at high doses (manuscript accepted to be published in Pulm. Pharm. Ther., submitted herewith as Appendix 7). In this study, patients inhaled 12 inhalations of budesonide/formoterol per day at a rate of 160 μg budesonide/4.5 μg

formoterol per inhaled dose, for a total daily dose of 1920 μg /54 μg. This dosage was intended to approximate the high end of the amount that might be inhaled by a patient using budesonide/formoterol on an "on demand" basis. (Declaration of Christer Hultquist, paragraph 10.)

It has been shown that asthma symptoms and concomitant use of rescue (quick relief) medication consistently increase several days before the onset of a clinical exacerbation (acute attack). (Am. J. Respir. Crit. Care Med. 160(2) (1999), 594-9.) When a formoterol/budesonide combination is prescribed for use on an "on demand" basis, as claimed, the patient will tend to use the combination more frequently in the period preceding a possible acute attack. This patient-initiated early increase in steroid dose will generally reduce the likelihood of the patient's asthma worsening, and tend to also reduce the likelihood of an acute attack that could require use of oral steroids or emergency treatment. Because the patient is instructed to use the combination on an "on demand" basis, in response to the patient's symptoms, the delay in increasing the dosage of steroid that is often caused by a patient's reluctance to consult a doctor and by time spent in obtaining an appointment can be avoided. When symptoms subside, the patient will naturally reduce the number of inhaled doses, and thus will not continue to receive an elevated dosage of steroid. (Declaration of Christer Hultquist, paragraph 11.)

Because the patient can vary the number of inhaled doses based on the patient's perception of his or her asthma symptoms, the overall amount of medication that the patient inhales over the course of a month or more may actually be less than would be required if the patient's maintenance therapy were simply adjusted up and left at the higher dosage. For example, a low maintenance dose and a temporary increase in dose for 1 or 2 weeks may have the potential to control asthma as effectively as a higher maintenance dose, resulting in a lower overall daily inhaled steroid dose. Moreover, a patient using the claimed treatment protocol may suffer from fewer acute attacks, and thus may require less frequent emergency care and other acute therapy such as oral steroids. Thus, prescribing the formoterol/budesonide combination for use on an "on demand" basis may decrease the cost of health-care utilization. (Declaration of Christer Hultquist, paragraph 12.)

Recent data support this theory. In a recently published study, patients using a formoterol/budesonide combination for maintenance therapy were instructed to increase their dose for up to 2 weeks when they found they were experiencing frequent exacerbations and/or night-time awakening due to nocturnal asthma, and then to decrease their dose when asthma control was regained. These patients maintained a health-related quality of life equivalent to that of patients receiving fixed dosing at a significantly higher overall dose (Haughney et al., ERS, Stockholm, 2002, poster P379 (Appendix 4) and Price et al., ERS, Stockholm, 2002, poster P2452 (Appendix 5). (Declaration of Christer Hultquist, paragraph 12.)

Further, in another study, patients using the claimed "on demand" treatment protocol suffered from fewer acute attacks than a control group on a fixed dose, and thus required less frequent emergency care and other acute therapy (Olsson et al., ERS, Stockholm, 2002, poster P2451 (Appendix 6). In this study, it was found that the mean total cost of asthma-related treatment per patient, over the course of the study, was 349 Euros for the "on demand" group versus 445 Euros for the control group. The mean total cost of the Symbicort® medication (the formoterol/budesonide combination) alone was 217 Euros for the "on demand" group versus 357 Euros for the control group. (Declaration of Christer Hultquist, paragraph 12.)

These results indicate that prescribing the formoterol/budesonide combination for use "on demand" may decrease the cost of health care while also improving the quality of life for asthma patients. (Declaration of Christer Hultquist, paragraph 12.)

It is clear from the information discussed above that the claimed treatment protocol represents an innovation that runs counter to the conventional wisdom at the time of Applicant's invention. Applicant's recognition that the formoterol/budesonide combination may be prescribed on an on demand basis, to provide both treatment and prevention, has the potential to provide significant benefits to asthma patients.

In view of the above, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant submits that this application is now in condition to be allowed. Early favorable action is solicited. Enclosed is a $156.00 check for excess claim fees. Please apply any other

Version with markings to show changes made

In the Title:

Please change the title to the following:

--NEW USE [OF A COMPOSITION COMPRISING FORMOTEROL AND BUDESONIDE FOR THE PREVENTION OR TREATMENT OF AN ACUTE CONDITION OF ASTHMA]--

In the claims:

Claim 13 has been amended as follows:

13. A method of prevention [or] and treatment of [an acute condition of asthma and/or intermittent asthma and/or episodes in chronic] asthma, which comprises

instructing a patient to inhale [, on demand, as determined by the patient based on the patient's symptoms, to provide short-term symptomatic relief of asthma symptoms,] an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

charges, including for any extension of time that may be required, or any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: December 10, 2002

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